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Developing an automated functional cardiotoxicity drug screening platform

Rie Kjær Christensen^{1,2}, Peder Skafte-Pedersen¹, Sandra Wilson¹, Niels Bent Larsen²

INTRODUCTION

Cardiotoxicity is a major challenge in drug development. Current cardiotoxicity testing relies heavily on ion channel measurements using patch clamp analysis on heart cells (cardiomyocytes). An automated functional cardiotoxicity drug testing method that extends beyond ion channel analysis has not yet been developed, but is required, as many cardiotoxic events do not correlate with ion channel behavior.

The key function in evaluating cardiac toxicity is cardiac mini-tissue contraction. The project aim is to develop an automated analysis platform with contracting mini-tissues in a multi-well format connected to a read-out system. A micro-molded platform manufactured using state-of-the-art 3D microprinting has shown proof of concept with model cells (mouse fibroblasts and myoblasts) cultured for up to 4 weeks.

PROCESS

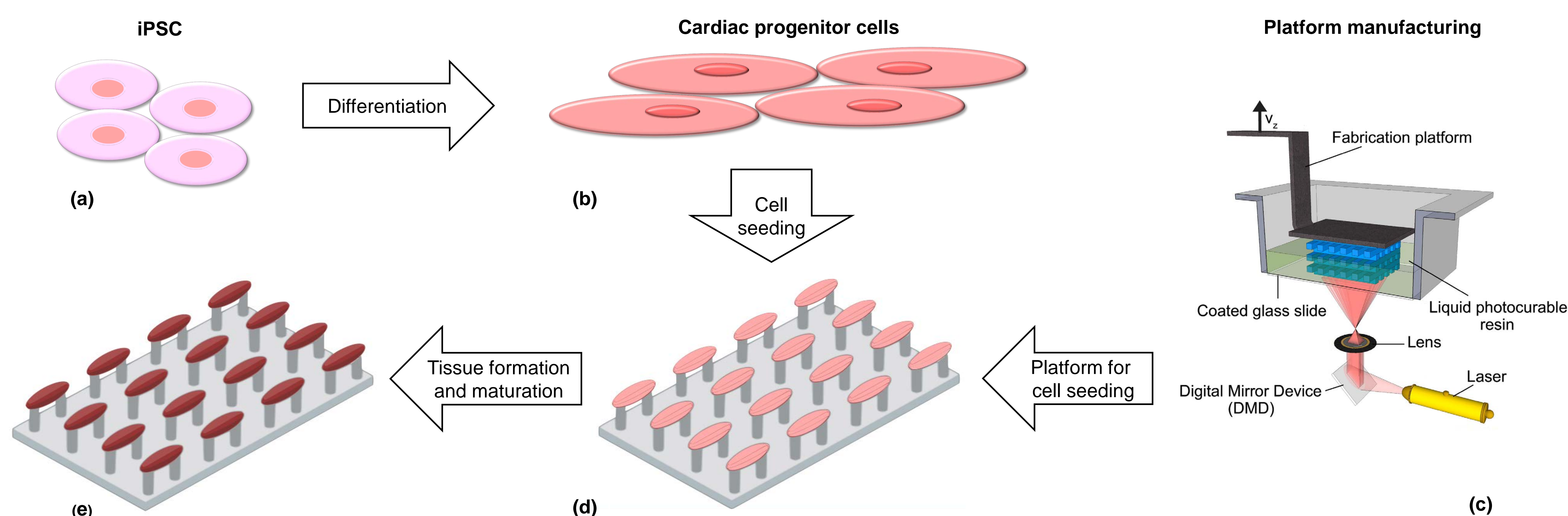


Fig. 1: Manufacturing process of the drug screening platform

(a) Induced pluripotent stem cells (iPSC) are grown in 2D and differentiated into cardiac progenitor cells in 0-15 days. (b) Cardiac progenitor cells are seeded onto the drug screening platform. (c) A stereolithographic method is used to produce the platform for cardiomyocyte cell culturing providing a fast and easy manufacturing process, [1],[2]. (d) After seeding cardiac progenitor cells onto the platform mini-tissues are formed and culturing is controlled to mature the mini-tissues into mature cardiomyocyte mini-tissues in day 15-35. (e) Drug screening platform with mature cardiomyocyte mini-tissues ready for drug screening protocols.

FUNCTIONALITY

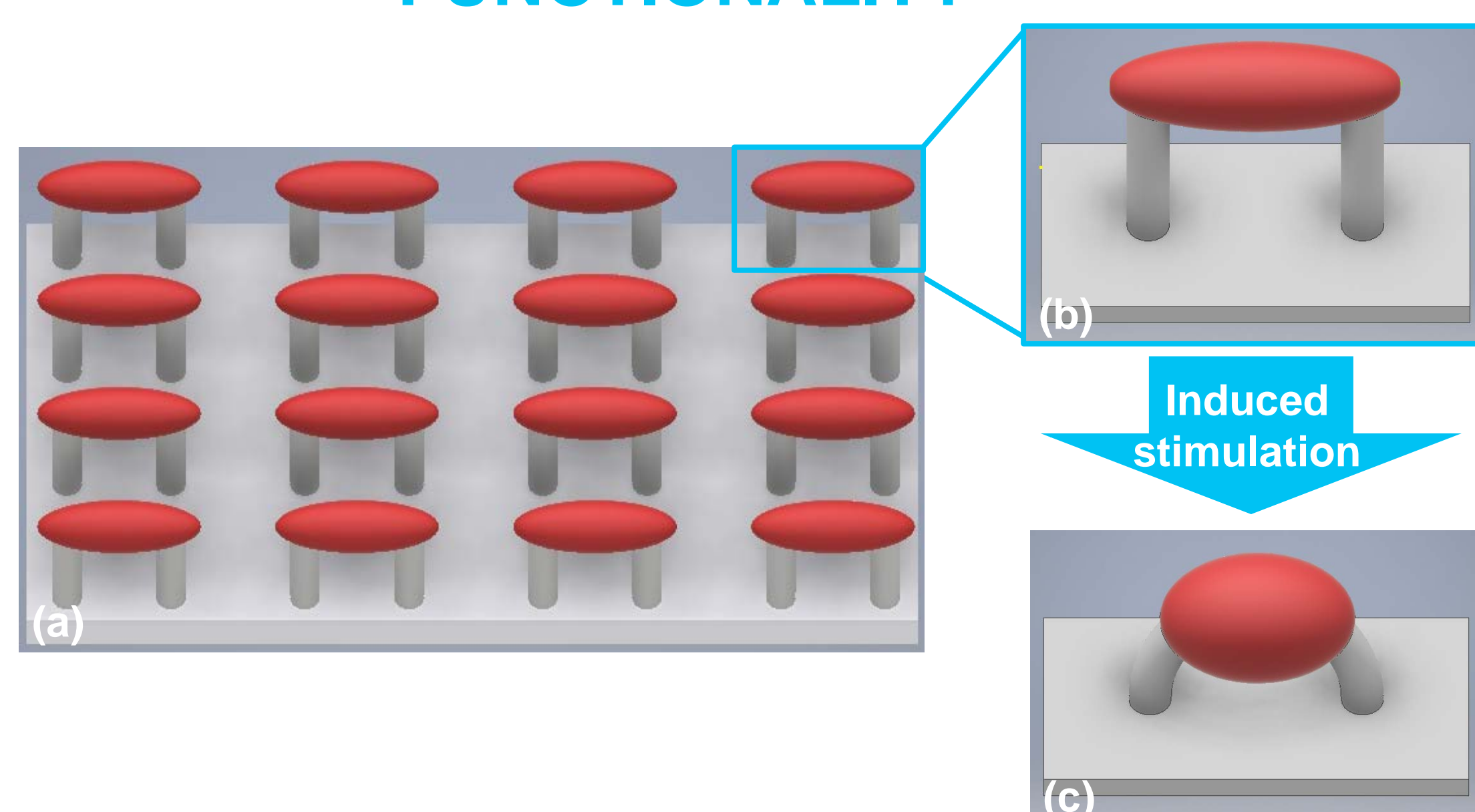


Fig. 2: Drug screening analysis platform

(a) An automated drug screening analysis platform to use for evaluating cardiotoxicity in a multiple construct configuration. By culturing in mechanically relevant conditions [2] it is possible to obtain a mature state of the cardiomyocyte that optimize the peak force generation. (b) The mini-tissues function independently (c) and will contract simultaneously based on an induced stimulation.

BACKGROUND FOR DEVELOPMENT

A lot of effort is going into drug development which is both time- and cost-intensive and robust methods to test cardiotoxic effects are still missing. In recent years development of a contractile mini-tissue in different shapes, configurations, sizes and dimensions have been investigated [3], [4], [5], [6], [7] as the contractile force is a good indicator of cardiomyocyte mini-tissue function. There is a tight correlation between culturing methods to reach maturity of the cardiomyocytes, stiffness, and contractile behavior, all of which has been considered in the presented drug screening platform.

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